I. Amendments to the Claims

This listing of claims shall replace all prior versions, and listings, of claims in the application.

Listing of Claims

Claim 1 (currently amended): An oral dosage form comprising

(i) an opioid agonist in releasable form, and

(ii) particles consisting of an opioid antagonist, a sequestering material and one or more additional pharmaceutically acceptable excipients,

wherein the sequestering material separates the antagonist from the agonist and substantially prevents the release of the antagonist from the dosage form which has been administered intact such that an amount of the antagonist released at 1 and 2 hours from the dosage form which has been administered intact is undetectable by High Performance Liquid Chromatography, and less than 15% by weight of the opioid antagonist is released within 36 hours after the administration of the intact dosage form, based on an in-vitro dissolution of the intact dosage form in a dissolution bath; ~~from the dosage form which has been administered intact is insufficient to produce a physiological effect of the antagonist in a human patient~~, and

a ratio of ~~an~~ the amount of the antagonist released from the dosage form after tampering to the amount of the antagonist released from the intact dosage form is about 4:1 or greater, based on the in-vitro dissolution of the dosage form at 1 hour in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C;

wherein the agonist and the particles are interdispersed and are not isolated from each other in two distinct layers.

Claim 2 (currently amended): An oral dosage form comprising

(i) an opioid agonist in releasable form, and

(ii) particles consisting of an opioid antagonist, a sequestering material and one or more additional pharmaceutically acceptable excipients,

wherein the sequestering material separates the antagonist from the agonist and substantially prevents the release of the antagonist from the dosage form which has been administered intact such that

an amount of the antagonist released at 1 and 2 hours from the dosage form which has been administered intact is undetectable by High Performance Liquid Chromatography, and less than 15% by weight of the opioid antagonist is released within 36 hours after the administration of the intact dosage form, based on an in-vitro dissolution of the intact dosage form in a dissolution bath; ~~from the dosage form which has been administered intact is insufficient to produce a physiological effect of the antagonist in a human patient~~, and

a ratio of an amount of the antagonist released from the dosage form after tampering to ~~an~~ the amount of the antagonist released from the intact dosage form is about 4:1 or greater, based on the in-vitro dissolution of the dosage form at 1 hour in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C;
wherein the particles are individually coated with the sequestering material.

Claim 3 (currently amended): An oral dosage form comprising

(i) an opioid agonist in releasable form, and

(ii) particles consisting of an opioid antagonist, a sequestering material and one or more additional pharmaceutically acceptable excipients,

the antagonist and the additional one or more pharmarmaceutically acceptable excipients dispersed in a matrix of the sequestering material,

the sequestering material separates the antagonist from the agonist and substantially prevents the release of the antagonist from the dosage form which has been administered intact such that

an amount of the antagonist released at 1 and 2 hours from the dosage form which has been administered intact is undetectable by High Performance Liquid Chromatography, and less than 15% by weight of the opioid antagonist is released within 36 hours after the administration of the intact dosage form, based on an in-vitro dissolution of the intact dosage form in a dissolution bath; ~~which has been administered intact is insufficient to produce a physiological effect of the antagonist in a human patient~~;

wherein a ratio of ~~an~~ the amount of the antagonist released from the dosage form after tampering to the amount of the antagonist released from the intact dosage form is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of the dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C [[;]].

Claim 4 (currently amended): An oral dosage form comprising

(i) an opioid agonist in releasable form,

(ii) particles consisting of an opioid antagonist, a sequestering material and one or more additional pharmaceutically acceptable excipients,

wherein the sequestering material separates the antagonist from the agonist and substantially prevents the release the antagonist from the dosage form which has been administered intact such that

an amount of the antagonist released at 1 and 2 hours from the dosage form which has been administered intact is undetectable by High Performance Liquid Chromatography, and less than 15% by weight of the opioid antagonist is released within 36 hours after the administration of the intact dosage form, based on an in-vitro dissolution of the intact dosage form in a dissolution bath; ~~which has been administered intact is insufficient to produce a physiological effect of the antagonist in a human patient,~~ and

a ratio of an amount of the antagonist contained in the intact dosage form to the amount of the antagonist released from the intact dosage form after 1 hour is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of the dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C;
wherein the agonist and the particles are interdispersed and are not isolated from each other in two distinct layers.

Claim 5 (currently amended): An oral dosage form comprising

(i) an opioid agonist in a releasable form;

(ii) particles consisting of an opioid antagonist, a sequestering material and one or more additional pharmaceutically acceptable excipients,

wherein the sequestering material separates the antagonist from the agonist and substantially prevents the release of the antagonist from the dosage form which has been administered intact such that

an amount of the antagonist released at 1 and 2 hours from the dosage form which has been administered intact is undetectable by High Performance Liquid Chromatography, and less than 15% by weight of the opioid antagonist is released within 36 hours after the administration of the intact dosage form, based on an in-vitro dissolution of the intact dosage form in a dissolution bath; ~~which has been administered intact is insufficient to produce a physiological effect of the antagonist in a human patient,~~

wherein ~~the amount of the antagonist released from the intact dosage form after 1 hour is less than an amount bioequivalent to 0.25 mg naltrexone and an~~ the amount of the antagonist released after 1 hour from the dosage form after tampering is an amount bioequivalent to 0.25 mg naltrexone or more, based on the dissolution at 1 hour of the dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C, and the agonist and the particles are interdispersed and are not isolated from each other in two distinct layers.

Claim 6 (currently amended): An oral dosage form comprising

(i) an opioid agonist in a releasable form;

(ii) particles consisting of naltrexone or a pharmaceutically acceptable salt thereof, a sequestering material and one or more additional pharmaceutically acceptable excipients,

wherein the sequestering material separates the naltrexone from the agonist and substantially prevents the release the naltrexone from the dosage form which has been administered intact such that

an amount of the naltrexone released at 1 and 2 hours from the dosage form which has been administered intact is undetectable by High Performance Liquid Chromatography, and less than 15% by weight of the naltrexone is released within 36 hours after the administration of the intact dosage form, based on an in-vitro dissolution of the intact dosage form in a dissolution bath; ~~which has been administered intact is insufficient to produce a physiological effect of the naltrexone in a human patient,~~ and

wherein ~~the amount of the naltrexone released from the intact dosage form after 1 hour is less than 0.25 mg and an~~ the amount of the naltrexone released after 1 hour from the dosage form after tampering is 0.25 mg or more, based on the dissolution at 1 hour of the dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C, and the agonist and the particles are interdispersed and are not isolated from each other in two distinct layers.

Claim 7 (currently amended): An oral dosage form comprising

(i) a therapeuticically effective dose of an opioid agonist;

(ii) particles consisting of an opioid antagonist, a sequestering material and one or more additional pharmaceutically acceptable excipients,

wherein the sequestering material separates the antagonist from the agonist and substantially prevents the release the antagonist from the dosage form such that

an amount of the antagonist released at 1 and 2 hours from the dosage form which has been administered intact is undetectable by High Performance Liquid Chromatography, and less than 15% by weight of the opioid antagonist is released within 36 hours after the administration of the intact dosage form, based on an in-vitro dissolution of the intact dosage form in a dissolution bath; ~~which has been administered intact is insufficient to produce a physiological effect of the antagonist in a human patient,~~ and

at 1 hour after oral administration, the intact dosage form releases not more than 25% of the antagonist, the dosage form providing analgesia and the released antagonist not affecting analgesic efficacy,

wherein the agonist and the particles are interdispersed and are not isolated from each other in two distinct layers.

Claim 8 (currently amended): An oral dosage form comprising:

(i) an opioid agonist in a releasable form;

(ii) particles of an opioid antagonist in substantially non-releasable form,

the particles consisting of the antagonist and **[[,]]** one or more additional pharmaceutically acceptable excipients, wherein one of the excipients is ~~and~~ a material that separates the

antagonist from the agonist and substantially prevents the release of the antagonist from the dosage form which has been administered intact such that

an amount of the antagonist released at 1 and 2 hours from the dosage form which has been administered intact is undetectable by High Performance Liquid Chromatography, and less than 15% by weight of the opioid antagonist is released within 36 hours after the administration of the intact dosage form, based on an in-vitro dissolution of the intact dosage form in a dissolution bath; ~~which has been administered intact is insufficient to produce a physiological effect of the antagonist in a human patient,~~

wherein the material is coated over the antagonist.

Claim 9 (currently amended): An oral dosage form comprising:

(i) an opioid agonist in a releasable form; and

(ii) particles of an opioid antagonist in substantially non-releasable form,

wherein the particles consist of the antagonist and one or more additional pharmaceutically acceptable excipients, one of the excipients being a sequestering material, wherein the antagonist is dispersed in a matrix consisting of ~~a~~ the sequestering material and the additional pharmaceutically acceptable excipients, and ~~that~~ separates the antagonist from the agonist and substantially prevents the release of the antagonist from the dosage form which has been administered intact such that

an amount of the antagonist released at 1 and 2 hours from the dosage form which has been administered intact is undetectable by High Performance Liquid Chromatography, and less than 15% by weight of the opioid antagonist is released within 36 hours after the administration of the intact dosage form, based on an in-vitro dissolution of the intact dosage form in a dissolution bath; ~~which has been administered intact is insufficient to produce a physiological effect of the antagonist in a human patient.~~

Claim 10 (previously presented): The oral dosage form of claim 1, wherein the ratio is 10:1 or greater.

Claim 11 (previously presented): The oral dosage form of claim 1, wherein the ratio is 50:1 or greater.

Claim 12 (previously presented): The oral dosage form of claim 1, wherein the ratio is 100:1 or greater.

Claim 13-14 (Cancelled)

Claim 15 (previously presented): The oral dosage form of claim 5, wherein the amount of antagonist released after 1 hour from the tampered dosage form is an amount bioequivalent to 0.5 mg naltrexone or more.

Claim 16 (cancelled)

Claim 17 (previously presented): The oral dosage form of claim 6, wherein the amount of antagonist released after 1 hour from the tampered dosage form is 0.5 mg naltrexone or more.

Claim 18 (cancelled)

Claim 19 (original): The oral dosage form of claim 1, wherein the opioid agonist is selected from the group consisting of morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, meperidine, methadone, oxymorphone, buprenorphine, fentanyl and derivatives thereof, dipipanone, heroin, tramadol, etorphine, dihydroetorphine, butorphanol, levorphanol, pharmaceutically acceptable salts thereof and mixtures thereof.

Claim 20 (original): The oral dosage form of claim 19, wherein the opioid agonist is selected from the group consisting of oxycodone, hydrocodone and pharmaceutically acceptable salts thereof.

Claim 21 (original): The oral dosage form of claim 1, wherein the opioid antagonist is selected from the group consisting of naltrexone, naloxone, nalmephene, cyclazocine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof.

Claim 22 (original): The oral dosage form of claim 21, wherein the opioid antagonist is selected from the group consisting of naltrexone, naloxone, nalmephene, pharmaceutically acceptable salts thereof and mixtures thereof.

Claim 23 (original): The oral dosage form of claim 22, wherein the opioid antagonist comprises naltrexone or a pharmaceutically acceptable salt thereof.

Claim 24 (previously presented): The oral dosage form of claim 2, wherein the sequestering material comprises a cellulose polymer or an acrylic polymer that is insoluble in the gastrointestinal tract and impermeable to the opioid antagonist contained within the coating.

Claim 25 (original): The oral dosage form of claim 24, wherein the cellulose polymer is selected from the group consisting of ethylcellulose, cellulose acetate, cellulose propionate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, and mixtures thereof.

Claim 26 (original): The oral dosage form of claim 24, wherein the acrylic polymer is selected from the group consisting of acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

Claim 27 (original): The oral dosage form of claim 1, wherein the dosage form provides sustained-release of the opioid agonist.

Claim 28 (original): The oral dosage form of claim 27, wherein the dosage form is a sustained-release tablet or a sustained-release capsule.

Claim 29 (currently amended): The oral dosage form of claim 2, wherein the particles are in the form of inert beads coated with the antagonist ~~and overcoated with the sequestering material~~.

Claim 30 (currently amended): The oral dosage form of claim 2, wherein the particles of are in the form of a granulation consisting of the antagonist, the one or more additional pharmaceutically acceptable excipients and the sequestering material.

Claim 31 (previously presented): The oral dosage form of claim 2, wherein the particles are dispersed in a matrix comprising the agonist.

Claim 32 (previously presented): The oral dosage form of claim 2, wherein the particles are contained in a capsule with the agonist.

Claim 33 (previously presented): The oral dosage form of claim 3, wherein the matrix is in the form of pellets.

Claim 34 (previously presented): The oral dosage form of claim 33, wherein the pellets are dispersed in a matrix comprising the agonist.

Claim 35 (previously presented): The oral dosage form of claim 33, wherein the pellets are contained in a capsule with the agonist.

Claim 36 (previously presented): The oral dosage form of claim 1, wherein the tampering is by crushing.

Claim 37 (previously presented): The oral dosage form of claim 27, wherein the tampering is in a manner as to obtain an immediate release of the agonist.

Claim 38 (previously presented): The oral dosage form of claim 1, wherein the tampering is to make the agonist available for inappropriate use.

Claim 39 (previously presented): The oral dosage form of claim 1, wherein the antagonist does not significantly affect analgesia provided by the agonist.

Claim 40 (previously presented): A method of decreasing the abuse of an opioid agonist in an oral dosage form, comprising incorporating the opioid agonist into a dosage form of claim 1.

Claim 41 (currently amended): A dosage form comprising:

(a) an opioid agonist;

(b) particles of naltrexone in a substantially non-releasable form;

wherein

the particles consist of the naltrexone **[[,]]** and one or more pharmaceutically acceptable excipients comprising a sequestering material, ~~and a~~

the sequestering material ~~which~~ separates the naltrexone from the agonist and sequesters the naltrexone such that

an amount of the naltrexone released at 1 and 2 hours from the dosage form which has been administered intact is undetectable by High Performance Liquid Chromatography, and less than 15% by weight of the naltrexone is released within 36 hours after said administration, based on an in-vitro dissolution of the intact dosage form in a dissolution bath; ~~which has been administered intact is insufficient to produce a physiological effect of the naltrexone in a human patient,~~ and

the agonist and the particles are at least partially interdispersed.

Claim 42 (original): The dosage form of claim 41 wherein the opioid agonist is oxycodone, codeine, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, salts thereof, or mixtures thereof.

Claim 43 (original): The dosage form of claim 42 wherein the opioid agonist is oxycodone hydrochloride.

Claim 44 (original): The dosage form of claim 42 wherein the opioid agonist is hydrocodone bitartrate.

Claim 45 (original): The dosage form of claim 42 wherein the opioid agonist is hydromorphone hydrochloride.

Claim 46 (original): The dosage form of claim 41 wherein at least part of the naltrexone is in a matrix.

Claim 47 (original): The dosage form of claim 41 wherein at least part of the naltrexone is in a coated bead.

Claim 48 (original): The dosage form of claim 41 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 15% by weight of the naltrexone *in vivo* after 36 hours.

Claim 49 (original): The dosage form of claim 48 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 8% by weight of the naltrexone *in vivo* after 36 hours.

Claim 50 (original): The dosage form of claim 49 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 1% by weight of the naltrexone *in vivo* after 36 hours.

Claim 51 (original): The dosage form of claim 41 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 3% by weight of the naltrexone *in vivo* after 1 hour.

Claim 52 (original): The dosage form of claim 41 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 1.0% by weight of the naltrexone *in vivo* after 1 hour.

Claim 53 (original): The dosage form of claim 41 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 0.5% by weight of the naltrexone *in vivo* after 1 hour.

Claim 54 (currently amended): A dosage form comprising:

(a) an opioid agonist;

(b) particles of an orally-bioavailable opioid antagonist in a substantially non-releasable form, the particles consisting of the orally-bioavailable opioid antagonist, one or more pharmaceutically acceptable excipients and

a sequestering material which separates the orally-bioavailable antagonist from the agonist,

wherein

an amount of the orally-bioavailable antagonist released at 1 and 2 hours from the dosage form which has been administered intact is undetectable by High Performance Liquid Chromatography, and less than 15% by weight of the opioid antagonist is released within 36 hours after the administration of the intact dosage form, based on an in-vitro dissolution of the intact dosage form in a dissolution bath; ~~which has been administered intact is insufficient to produce a physiological effect of the orally-bioavailable antagonist in a human patient~~.

Claim 55 (original): The dosage form of claim 54 wherein the agonist and antagonist are at least partially interdispersed.

Claim 56 (original): The dosage form of claim 54 wherein the orally-bioavailable opioid antagonist is naltrexone, or a salt thereof.

Claim 57 (original): The dosage form of claim 54 wherein the opioid agonist is oxycodone, codeine, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, or salts thereof or mixtures thereof.

Claim 58 (original): The dosage form of claim 54 wherein at least part of the antagonist is in a matrix.

Claim 59 (original): The dosage form of claim 54 wherein at least part of the antagonist is in a coated bead.

Claim 60. (cancelled)

Claim 61 (original): A method of treating pain comprising administering to a human patient a dosage form of claim 1.

Claim 62 (currently amended): The oral dosage form of any one of claims 1, 2, 3, 4, 5, 7, 19, 21, 29, 30, 31, 32, 33, or 34, wherein the amount of the antagonist released at 4 hours from the dosage form which has been administered intact is undetectable by High Performance Liquid Chromatography ~~the particles are adapted to release less than 15% by weight of the antagonist within 36 hours after administration of an intact dosage form~~.

Claim 63 (currently amended): The oral dosage form of any one of claims 1, 2, 3, 4, 7, 8, 9, 14, 19, 21, 25, 26, 27, 29, 30, 31, 32, 33, 34, 41, 42, 48, 54, 55, 56, 57, 58, or 59, wherein an amount of the antagonist released from the dosage form which has been administered intact is insufficient to produce an antagonistic effect of the antagonist ~~less than an amount bioequivalent to 0.125 mg of naltrexone, based on the in-vitro dissolution of the dosage form at 1 hour in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C~~.

Claim 64 (currently amended): The oral dosage form of claim 62, wherein ~~an~~ the amount of the antagonist released at 12 hours from the dosage form which has been administered intact is undetectable by High Performance Liquid Chromatography ~~less than an amount bioequivalent to 0.125 mg of naltrexone, based on the in-vitro dissolution of the dosage form at 1 hour in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C~~.

Claim 65 (currently amended): The oral dosage form of any one of claims 1, 2, 3, 4, 5, 7, 8 or 9, wherein the amount of the opioid antagonist released from the dosage form which has been subjected to tampering will produce an antagonistic ~~a physiological~~ effect of the antagonist in a human patient.

Claim 66 (currently amended): The oral dosage form of claim 65, wherein the antagonistic ~~physiological~~ effect is ~~is~~ prevention of development of physical dependence to opioids.

Claim 67 (currently amended): The oral dosage form of claim 6, wherein the amount of the naltrexone released from the dosage form which has been subjected to tampering will produce an antagonistic ~~a physiological~~ effect of the naltrexone in a human patient.

Claim 68 (currently amended): The oral dosage form of claim 41, wherein the amount of the naltrexone released from the dosage form which has been subjected to tampering will produce an antagonistic ~~a physiological~~ effect of the naltrexone in a human patient.

Claim 69 (currently amended): The oral dosage form of claim 54, wherein the amount of the orally-bioavailable opioid antagonist released from the dosage form which has been subjected to tampering will produce an antagonistic ~~a physiological~~ effect of the orally-bioavailable opioid antagonist in a human patient.

Claim 70 (previously presented): The oral dosage form of claim 2, wherein the sequestering material is an acrylic polymer.

Claim 71 (previously presented): The oral dosage form of claim 3, wherein the sequestering material is an acrylic polymer.

Claim 72 (previously presented): The dosage form of claim 8, wherein the material is an acrylic polymer.

Claim 73 (previously presented): The dosage form of claim 9, wherein the material is an acrylic polymer.